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| Application Number | 09/991,150 |
| Filing Date | NOVEMBER 16, 2001 |
| First Named Inventor | KEVIN P. BAKER |
| Group/Art Unit | 1646 |
| Examiner Name | KEMMERER, ELIZABETH |
| Total Number of Pages in This Submission: 7 | Attorney Docket Number: 39780-2730 P1C48 |

**ENCLOSURES** *(check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
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  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Information Disclosure Statement
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- ☐ Response to Missing Parts/ Incomplete Application
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- ☐ Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, by Assignee to Exclusion of Inventor Under 37 C.F.R. §3.71 With Revocation of Prior Powers
- ☐ Terminal Disclaimer
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- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ **APPEAL COMMUNICATION TO GROUP** ***(APPEAL NOTICE, BRIEF, REPLY BRIEF)***
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| | | | |
|---|---|---|---|
| Firm or Individual name | HELLER EHRMAN LLP | GINGER R. DREGER (Reg. No. 33,055) | |
| | 275 Middlefield Road, Menlo Park, California 94025 | Telephone: (650) 324-7000 | Facsimile: (650) 324-0638 |
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| In re application of: | ) | Examiner: Kemmerer, Elizabeth |
| Kevin P. BAKER, *et al.* | ) | Art Unit: 1646 |
| Application Serial No. 09/991,150 | ) | Confirmation No: 4272 |
| Filed: November 16, 2001 | ) | Attorney's Docket No. 39780-2730 P1C48 |
| For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME** | ) | **Customer No. 35489** |

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## ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
## APPELLANTS' REPLY BRIEF

**MAIL STOP APPEAL BRIEF - PATENTS**
Commissioner for Patents -
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On September 16, 2004, the Examiner made a final rejection to pending Claims 124, 129-131 and 135-145. A Notice of Appeal was filed on January 27, 2005, and Appellants' Appeal Brief was filed July 26, 2005.

An Examiner's Answer was mailed on October 5, 2005. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer. This Reply Brief is accompanied by a Request for Oral Hearing.

## ARGUMENTS

***Claim Rejections Under 35 U.S.C. §101 and § 112, First Paragraph***

Concerning the rejection of Claims 124, 129-131 and 135-145 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility, in her Answer, the Examiner argues that "the data do not support the implicit conclusion of the specification that PRO341 genomic DNA shows a positive correlation with lung cancer, much less that the levels of PRO341 genomic DNA would be diagnostic as such." The Examiner cites the following arguments in support of this conclusion:

(1) the genomic DNA encoding PRO341 had a ΔCt value for three out of fourteen lung tumor samples. Genomic DNA encoding PRO341 was not amplified in any of the fourteen colon tumor samples;

(2) very few ΔCt values were obtained that were at least 2;

(3) referring to three publications Livak *et al.*, Heid *et al.* and Pennica *et al.* cited in the Goddard Declaration, the Examiner says that "none of Livak *et al.*, Heid *et al.*, nor Pennica *et al.*, appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors;"

(4) even if the data demonstrated a slight increase in copy number of PRO341 genomic DNA in primary tumors, such would not be indicative of a use of the claimed nucleic acids as diagnostic agents, since: (a) the data are not corrected for aneuploidy, (b) Hittelman (2001) teaches that precancerous lung epithelium is often aneuploid, therefore, based on the differential gene expression data one of ordinary skill would not conclude that PRO341 genomic DNA is amplified in cancerous lung epithelium more than damaged (non-cancerous) lung epithelium; (c) an argument that PRO341 would still be a marker for at least precancerous or damaged lung epithelium would not prevail since it is "not suggested by the specification as originally filed and is not well-established in the prior art."

The same arguments are cited in support of the rejection under 35 U.S.C. §112, first paragraph, for alleged lack of enablement for how to use the invention.

The Examiner's arguments will be addressed in the order they are listed above.

(1) In making the rejection that "only three out of fourteen lung tumor samples tested positive" and "PRO341 was not amplified in any of the fourteen **colon** tumor samples" (emphasis

added), the Examiner seems to indicate that a tumor marker is patentable only if the marker tests positive in a statistically high number of samples compared to the total number of samples tested or if the tumor tests positive in every tissue type that was studied. However, this is not legally correct. Neither the M.P.E.P. nor the Utility Guidelines require that it is necessary for the Appellant to show a positive result in most or a larger percentage of the tissue samples studied in order to make an assertion of utility, nor are they needed to show that the tumor marker identifies cancers of various tissues types, *e.g.,*: lung, colon, etc. The above remarks by the Examiner are a clear indication that the Examiner applies a standard that might be appropriate, if the issue at hand were the regulatory approval of a diagnostic assay based on the overexpression of PRO341 in lung tumor, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA reviewing an application for a new diagnostic assay will indeed ask for actual numerical data, statistical analysis, and other specific information before a diagnostic assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to a diagnostic utility as well. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Furthermore, as indicated previously, it is well-accepted in the art that not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, even if the association of a tumor marker with a particular type of tumor lesion is rare, or, even if the occurrence of a particular kind of tumor lesion itself is rare, since such markers identifying rare tumors, they have great value in tumor diagnosis, and consequently, in tumor prognosis. The ΔCt values for PRO341 of at least 1.12-1.33 ΔCt units, which correspond to $2^{1.12}$ -$2^{1.33}$- fold amplification or 2.173 to 2.514 fold amplification in primary lung tumors, were considered significant according

to the Goddard declaration. The skilled artisan would know the value and utility of rare tumor markers. Further, Appellants need not show that DNA was amplified in colon tumors as well for an assertion of utility.

(2) The discussions above under Point (1) also address the rejection that "very few ΔCt values were obtained that were at least 2."

(3) The Examiner says that "none of Livak *et al.*, Heid *et al.*, nor Pennica *et al.*, appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors" in rejecting the Goddard Declaration. Appellants strongly disagree. The above references were cited in the Goddard Declaration to show that quantitative TaqMan PCR assay is a well-known and widely used assay in the art for studying gene amplification in various cancers. For instance, the Goddard declaration clearly says that:

> "the quantitative TaqMan PCR assay is exemplified by the fcllowing scientific publications: Pennica *et al.*, Proc. Natl. Acad. Sci. USA 95(25):14717-14722 (1998) (Exhibit E); Pitti *et al.*, Nature 396(6712):699-703 (1998) (Exhibit F) and Bieche *et al.*, Int. J. Cancer 78:661-666 (1998) (Exhibit G), the first two of which I am co-author. In particular, Pennica *et al.* have used the quantitative TaqMan PCR assay to study relative gene amplification of WISP and c-myc in various cell lines, colorectal tumors and normal mucosa. Pitti *et al.* studied the genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer, using the quantitative TaqMan PCR assay. Bieche *et al.* used the assay to study gene amplification in breast cancer."

Therefore, Dr. Goddard did not rely on the above mentioned references for determining whether "a 2-fold amplification is significant." The Examiner has misrepresented of the actual purpose for presenting these references in the Goddard Declaration. Instead, the opinions expressed in the Goddard Declaration regarding the significance of the 2-fold amplification is based on Dr. Goddard's own scientific experience and factual findings. By making this rejection, the Examiner seems to disregard the expert's opinion based on her own personal disagreement over the significance or meaning of the facts offered, without solid support or scientific showing for her opinion(s). Appellants respectfully remind the Examiner that the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which states, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; **it is improper to disregard the opinion solely because of a disagreement over the**

**significance or meaning of the facts offered**" (emphasis added). Therefore, barring solid scientific evidence from the art as that show why a 2-fold amplification of DNA in the TaqMan PCR assay would not be considered significant by one skilled in the art, the basis for this utility rejection is flawed and is inappropriate.

(4) Appellants had discussed the Examiner's point on aneuploidy and the Hittelman reference in detail in their Appeal brief filed July 26, 2005. Appellants had submitted that even if the observed gene amplification for PRO341 were due to aneuploidy (which Appellants do not concede to), since aneuploidy itself is associated with early detection of cancer, the PRO341 gene would still be useful as a biomarker, and this view is supported by the teachings of Hittelman. For instance, Hittelman clearly teaches on page 2, fourth paragraph, line 3 "it is important to identify individuals **at significantly increased cancer risk** who might best benefit from different types of intervention(emphasis added)." However, the Examiner indicates that, that 'a marker is useful for precancerous or damaged lung epithelium' is not available in the Appellants' specification as filed. Appellants point out that, this point was well-established in the prior art, at the effective date of filing of this application, contrary to what the Examiner contends. Appellants submit that there was a shift towards detecting pre-malignant and early-malignant lesions of lung and associating aneuploidy, precancerous lung or damaged lung epithelium and early lung cancer detection in the prior art. For instance, it was known that lung cancer was the end-stage of multi-step carcinogenesis, and in most cases, was driven by genetic and epigenetic damage caused by chronic exposure to tobacco carcinogens. It was also known that preneoplastic cells contained several molecular genetic abnormalities identical to those found in overt lung cancer cells, and well before the effective filing date of **July 9, 1998** of the present application, the therapeutic paradigm and focus had already shifted from targeting only clinically verified lung cancer toward targeting pre-malignant and early-malignant lesions. Furthermore, the prospects of lung cancer screening had become more meaningful as a consequence of developments in biology and radiology and better possibilities to define high risk populations most suitable for lung cancer screening. Articles in lung cancer and early- lung cancer detection published around and before July 9, 1998 collectively lent support to the view that it was important to detect, diagnosis and treat early lung cancer. Therefore, one skilled in the art of oncology, at the effective date of filing of the instant application, would have known, based on the teachings of the instant specification

and the well-established art in the lung cancer, how to use the instant PRO341 gene for the diagnosis of certain lung cancers, without undue experimentation.

For the reasons given above, Appellants respectfully submit that the Examiner has not established a *prima facie* showing of lack of utility based on the rejections in the Examiner's answer and therefore, the Patent Office has failed to meet its initial burden of proof. Accordingly, this rejection under 35 U.S.C. §101 and §112, first paragraph should be withdrawn.

## CONCLUSION

For the reasons given above, Appellants submit that the gene amplification assay disclosed in Example 170 of the specification, and the advanced state of the art in oncology, provide at least one patentable utility for the PRO341 nucleic acids of Claims 124, 129-131 and 135-145, and that one of ordinary skill in the art would understand how to use the claimed polypeptides and would have found such testing routine and not 'undue.' Therefore, Claims 124, 129-131 and 135-145 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C48**).

Respectfully submitted,

Date: December 5, 2005

By: _____
Ginger R. Dreger (Reg. 33,055)

**HELLER EHRMAN LLP**
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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